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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,299	01/17/2002	Michael A. Zasloff	MZ 100	5008

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HENRY E. MILLSON JR.
675 GOLDEN HAWK DRIVE
PRESCOTT, AZ 86301

EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/053,299	ZASLOFF ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18,25,31,32,34 and 41-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18,25,31,32,34 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Amendment, Response and Applicant's Arguments/Remarks, all filed 03/18/05 is acknowledged.

Claims 1-16, 18, 25, 31, 32, 34 and 41-44 are pending. Claims 1, 5, 6, 9-11, 18 and 32 have been amended. New claims 41-44 have been added. (Claims 17, 19-24, 26-30, 33 and 35-40 have been cancelled). Claims 1-16, 18, 25, 31, 32, 34 and 41-44 are rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 18, 25, 31, 32, 34 and 41-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of

the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation

(1) The nature of the invention:

The nature of the invention is directed to a method of blocking microbial adherence to a eukaryotic cell surface by applying to said surface a pharmaceutically acceptable composition consisting essentially of isoleucine in a microbial blocking quantity.

(2) The state of the prior art:

The prior art teachings provide for one or more of amino acids (*i.e.*, isoleucine), physiologically acceptable salts of amino acids, oligopeptides and polypeptides as active ingredients for treating conditions of fungal vaginitis and gingivitis. The composition can be in various forms, which include, tablets, capsules, lotions, creams, gels, ointments, aerosol sprays, emulsions, drops and suppositories.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

The predictability of the art is high. Prior art formulations recognize compositions comprising isoleucine for use in treating microbial infections, such as fungal infections. Prior art (US 6,770,306) teaches amino acids, such as isoleucine for treating vaginal infections and teaches that isoleucine can be used in combination with antifungal drugs for suppressing and killing fungi and enhance the treatment effect of the composition for fungal vaginitis.

(5) The breadth of the claims:

The claims are quite broad. The claims permit the blockage of any microbe. The specification does not define nor limit the term 'microbe' or 'microbial', and thus is broad in the sense that it includes multiple microbes (*i.e.*, bacteria, viruses, fungi, etc.).

(6) The amount of direction or guidance presented:

The specification filed 01/17/02, discloses 'preventing or treating' infection or other medical conditions by a direct effect of isoleucine on the adhesion of detrimental microbes to epithelial and other eukaryotic cells (pg. 5, lines 8-10). It is unclear to the Examiner as to how one single amino acid, (in this instance, isoleucine) can treat or prevent an entire group of microbes. The term 'preventing' on page 5, line 8 of the instant specification implies a cure. The specification provides no guidance on how the treatment or prevention of microbes can be provided through the use of one single amino acid, isoleucine.

(7) The presence or absence of working examples:

The working examples are insufficient to establish the method of blocking microbial adherence to eukaryotic cells. The examples are too limited, with no scientific data being presented. The examples provide for a very limited and small population being tested. The examples are distinct from the scope of the claims and there are no formulations of the claims presented. For instance, Example 1 on page 15 demonstrates a pure crystalline powder applied directly to the gums for gingival infections. Example 2 provides for the treatment of infectious diarrhea using isoleucine, with only three individuals naturally inoculated by a common agent. Example 3 provides for the amelioration of irritable bowel syndrome, employing only two women for the experiment. Example 4 demonstrates treatment of bacterial vaginosis of a 26-year-old female, wherein isoleucine was administered as a powder twice daily. Therefore, the working examples are insufficient to establish the instant method of blocking microbial adherence.

(8) The quantity of experimentation necessary:

The instant invention provides for a method of blocking microbial adherence to eukaryotic cells by applying isoleucine to the cells in a microbial blocking quantity. Microbes include among others, bacteria, viruses, fungi, molds, etc. When the above factors are weighed together, it is the position of the Examiner that the instant invention would require 'undue' and painstaking experimentation to arrive at the instant invention to determine which particular microbes would be positively affected by the single amino acid, isoleucine.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 18, 25, 31, 32, 34 and 41-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim a method of blocking microbial adherence to eukaryotic cells by applying a composition consisting essentially of isoleucine to the cells in a microbial blocking quantity. The process steps and written description are insufficient and have not been presented in such a way as to allow one of ordinary skill in the art to understand and practice the invention. No specific formulations, specific amounts and specific procedures or administrations are set forth to allow one of ordinary skill to know how to perform a method of blocking microbial adherence to eukaryotic cells by applying an isoleucine composition.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-6, 8-16, 18, 25 and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen (US 6,607,711 B2).

Applicants claim a method of blocking microbial adherence to a eukaryotic cell surface in a mammal by applying to said surface a pharmacologically acceptable composition consisting essentially of isoleucine present in a microbial blocking quantity.

The Examiner has interpreted the instant claims as being drawn to a method of blocking microbial adherence to eukaryotic cells by applying a composition, which permits mixtures of amino acids, although Applicant's specification prefers only one amino acid, isoleucine (see for example, pg. 2, lines 1-4 and 12-15).

Pedersen ('711) teaches a mouth hygienic composition and methods useful for the treatment of gingivitis, plaque formation and halitosis or bad breath wherein the composition comprises a metal ion and an essential amino acid, such as isoleucine (see reference column 1, lines 5-12); (col. 6, lines 17-25 and Abstract). The mouth hygiene composition also includes antimicrobial agents, such as cetyl pyridinium chloride; fluoride compounds such as sodium fluoride and sodium monofluorophosphate and saliva-inducing/sweetening agents such as xylitol (col. 7, lines 56-60); (col. 8, lines 35-46). The composition used for release in the oral cavity is suitably in the form of a lozenge, a troche, a chewing gum, toothpaste, a liquid mouth-rinsing composition, a sweet and a resoriblet (col. 8, lines 19-25).

Pedersen teaches that the mouth hygiene composition comprises chelates of a metal ion to preferably one, two or three amino acids (col. 5, lines 14-16). According to Pedersen, one aspect of his invention is largely due to the fact that plaque formation in the oral cavity is due to microbial growth and activity. By reacting with the sulfur-containing amino acids in the oral cavity, the metal ion moiety of the chelate significantly reduces the microbial growth potential which in turn is likely to lead to a reduced plaque formation (col. 8, lines 3-9).

The examples at columns 11-14 demonstrate various embodiments of the invention wherein zinc amino acid chelates were employed in combination with adjutants, wherein the end results obtained indicated an effective reduction and inhibition of halitosis.

Applicants in claims 2-4 and 10-13 recite desire ranges of 'microbial blocking quantities' and desired ranges of 'isoleucine'. Pedersen does not teach Applicant's claimed ranges. However, it is the position of the Examiner that, absent any showing of criticality accruable from the instant ranges, it would have been deemed obvious to one of ordinary skill in the art at the time the invention was made to determine suitable ranges or amounts of through the use of routine or manipulative experimentation to obtain the best possible results, as these are indeed variable parameters within the art. Moreover, the Examiner points out that generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). In the instant case, no criticality has been observed in the claimed concentration ranges since Applicants have not demonstrated any unexpected and/or unusual results, which accrue from the instantly claimed ranges. The prior art expressly desires and achieves therapeutically effective results for the treatment of gingivitis, halitosis and plaque formation through the combined use of amino acids, particularly isoleucine, antimicrobials, fluorides and sweetening/saliva-inducing agents (*i.e.* xylitol). Therefore, in view of the prior art teachings of Pedersen, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

This rejection is maintained and applied to newly added claims 41-44. Pedersen teach methods useful for the treatment of gingivitis, plaque formation and halitosis or bad breath

wherein the composition comprises a metal ion and an essential amino acid, such as isoleucine (see reference column 1, lines 5-12); (col. 6, lines 17-25 and Abstract).

Claims 1-6, 8-13, 18, 25, 31, 32, 34 and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeng (US 6,770,306 B1).

Applicants claim a method of blocking microbial adherence to a eukaryotic cell surface in a mammal by applying to said surface a pharmacologically acceptable composition consisting essentially of isoleucine present in a microbial blocking quantity.

The Examiner has interpreted the instant claims as being drawn to a method of blocking microbial adherence to eukaryotic cells by applying a composition, which permits mixtures of amino acids, although Applicant's specification prefers only one amino acid, isoleucine (see for example, pg. 2, lines 1-4 and 12-15).

Zeng ('306) teaches a pharmaceutical composition and method for treating vaginitis, especially fungal vaginitis and reducing vaginal acidity consisting essentially of an effective amount of amino acids and physiologically acceptable salts of amino acids, wherein suitable amino acid compounds include isoleucine of L-type (see Abstract); (column 4, lines 11-26); (Claim 1).

The pharmaceutical composition can be in the form of lotion, drops, aerosol spray, suspension, emulsion, creams, tablets, suppository, gelate, ointments, microcapsules, sustained release dosage forms or any other acceptable vaginal local drug forms (see col. 4, lines 50-55) and Claim 5.

According to Zeng, the composition can also contain anti-fungal drugs of an effective amount, used for suppressing and killing fungi, and enhance the treatment effect of the composition of the invention for fungal vaginitis. The composition can also contain one or more pharmaceutically acceptable carriers (col. 3, lines 57-59); (col. 5, lines 32-39).

Zeng teaches that the amino acid total content is preferably is 30-350 mmol/L (col. 5, lines 1-5). The weight/volume content (W/V) of the composition refers to grams of the specific component in 100 milliliters of the composition. In liquid compositions, amino acids can be dissolved or suspended in one or more kinds of pharmaceutical carriers (col. 5, lines 46-52). The total dosage of amino acids as active components per day are preferred in amounts of 0.01-1.5 g, administered in one or more times (col. 6, lines 55-60).

The examples at columns 7-12 demonstrate compositions containing amino acids in various formulations and amounts. Example 1 at column 7 for instance, demonstrates the use of composite amino acids in an amount of 3.0g (glutamic acid, aspartic acid, isoleucine, methionine, phenylalanine, tyrosine, valine, leucine and praline of 2.36 mmol each), yeast extract powder, sodium bicarbonate and xanthan gum in a homogeneous mixture.

The amounts of isoleucine taught by the prior art are overlapping amounts, which read on the instant ranges and amounts claimed. Zeng does not expressly teach Applicant's ranges of 'microbial blocking quantities' recited in instant claims 2-4. However, absent any showing of criticality accruable from the instant ranges, it would have been deemed obvious to one of ordinary skill in the art at the time the invention was made to determine suitable ranges or amounts of through the use of routine or manipulative experimentation to obtain the best possible results, as these are variable parameters within the art. Moreover, as delineated above, generally,

differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller,* 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955). Applicants have not demonstrated any unexpected and/or unusual results, which accrue from the instantly claimed ranges. The prior art explicitly teaches formulations consisting essentially of amino acids, which include isoleucine, used for the effective treatment of vaginitis, especially fungal vaginitis. The prior art teaches the incorporation of the same active ingredient (isoleucine), employed in similar amounts, used in the same field of endeavor and to treat the same problems (fungal infections). Therefore, in view of the prior art teachings of Zeng, the instant invention, when taken as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

This rejection is maintained and applied to newly added claims 41-44. Zeng teaches methods for treating vaginitis, especially fungal vaginitis and reducing vaginal acidity consisting essentially of an effective amount of amino acids and physiologically acceptable salts of amino acids, wherein suitable amino acid compounds include isoleucine of L-type (see Abstract); (column 4, lines 11-26); (Claim 1).

Response to Arguments

Applicant's arguments filed 03/18/05 have been fully considered but they are not persuasive.

Applicant argued regarding the 35 U.S.C. 112, 1st paragraph rejection of claims 1-16, 18, 25, 31, 32 and 34 stating, "The microbial blocking quantities that can be used to obtain this effect are set forth in lines 16-19 on page 2. Any physician can readily determine dosage quantity needed to obtain the above microbial blocking quantities."

Applicant's arguments have been considered, but were not found persuasive. The microbial blocking quantities argued by Applicants are not recited in the generic claims.

Applicant argued, "In addition, on page 7, first paragraph, a readily implemented method for determining an effective dose of isoleucine is set forth in clear language."

Arguments were not persuasive. The instant process is not enabled to demonstrate as to how to measure and the identity of the specific microbes.

Applicant argued, "Furthermore, dosage forms for administration of isoleucine are set forth throughout the specification, including the use of isoleucine as the only pharmacologically active component."

Applicant's arguments were not persuasive because the dosage forms are not enabling since the formulations used to determine the percentages have not been described. The data presented is insufficient to establish the instant method for blocking microbial adherence. The claims are not limited to the specific scopes argued by Applicant. Regarding factors 1 (nature of the invention), 2 (state of the prior art), 4 (predictability or unpredictability of the art), 6 (amount of direction or guidance presented) and 7 (presence or absence of working examples), it is the Examiner's position that these factors are sufficient to establish that Applicant has not overcome the enablement burden. It is not necessary that all of the factors be in the Examiner's favor, but here, the majority of the factors establish non-enablement.

Applicant argued regarding the 35 U.S.C. §103(a) rejection of claims 1-16, 18 and 25 over Pedersen (US '711) stating, "As noted by the Examiner, Pedersen's compositions require the use of chelates of a metal ion, in which it is the metal ion that reduces microbial growth potential."

Applicant's arguments were not persuasive. The presence of metal ions is considered equivalent to Applicant's invention (see for instance, instant claim 11).

Applicant argued regarding the 35 U.S.C. §103(a) rejection of claims 1-13, 18, 25, 31, 32 and 34 over Zeng (US '306) stating, "Claim 1, component (B) excludes other amino acids as an additional pharmacologically active substance. The claims as amended exclude mixtures of amino acids. Zeng teahes amino acid mixtures as neutralizing agents, that has nothing to do with the blocking of cell surfaces to block microbial adherence."

Applicant's arguments were not persuasive because the mixtures function in a similar manner. Burden is on Applicant to show that the additional ingredients would be detrimental. Note that instant claim 11 permits additional pharmacological agents. Since claim 11 was processed as the same invention, the term 'consisting essentially of' would not exclude the additional active agents. For the reasons advanced above, Applicant's arguments were not persuasive.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

H. N. Sheikh H.N.S.

Patent Examiner

Art Unit 1615

May 31, 2005

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600